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Association between type 2 diabetes genetic susceptibility loci and visceral and subcutaneous fat area as determined by computed tomography

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## ABSTRACT

Visceral fat accumulation plays an important role in the development of several metabolic disorders, such as type 2 diabetes, dyslipidemia, and hypertension. New genetic loci that contribute to the development of type 2 diabetes have been identified by genome-wide association studies. In order to examine the association of type 2 diabetes susceptibility loci and visceral fat accumulation, we genotyped 1279 Japanese subjects (556 men and 723 women), who underwent computed tomography (CT) for measurements of visceral fat area (VFA) and subcutaneous fat area (SFA) for the following single nucleotide polymorphisms (SNPs): *NOTCH2* rs10923931, *THADA* rs7578597, *PPARG* rs1801282, *ADAMTS9* rs4607103, *IGF2BP2* rs1470579, *VEGFA* rs9472138, *JAZF1* rs864745, *CDKN2A/CDKN2B* rs564398 and rs10811661, *HHEX* rs1111875 and rs5015480, *TCF7L2* rs7901695, *KCNQ1* rs2237892, *KCNJ11* rs5215 and rs5219, *EXT2* rs1113132, rs11037909, and rs3740878, *MTNR1B* rs10830963, *DCD* rs1153188, *TSPAN8/LGR5* rs7961581, and *FTO* rs8050136 and rs9939609. None of the above SNPs were significantly associated with VFA. The *FTO* rs8050136 and rs9939609 risk alleles exhibited significant associations with body mass index (BMI) ( $P = 0.00088$  and  $P = 0.0010$ , respectively) and SFA ( $P = 0.00013$  and  $P = 0.00017$ , respectively). No other SNPs were significantly associated with BMI or SFA. Our results suggest that 2 SNPs in the *FTO* gene are associated with subcutaneous fat accumulation. The contributions

of other SNPs are inconclusive because of a limitation of the sample power.

Key words: *FTO*, visceral fat area, subcutaneous fat area, computed tomography, type 2 diabetes,

Japanese subjects

## INTRODUCTION

Metabolic syndrome is defined by 4 conditions: visceral fat obesity, impaired glucose tolerance, dyslipidemia, and hypertension.<sup>1</sup> Various adipocytokines secreted from adipocytes have been identified and shown to cause dyslipidemia, hypertension, and insulin resistance.<sup>2, 3</sup> Previous studies on adipocytokines indicate that visceral fat obesity plays a central role in the development of metabolic syndrome. The determination of visceral fat mass is performed in terms of waist circumference, waist-hip ratio, or visceral fat area (VFA). Waist circumference and waist-hip ratio are commonly used because they are simple and convenient. However, VFA measured using computed tomography (CT) is one of the most precise methods to assess fat distribution.<sup>1, 4, 5</sup> There is an abundance of evidence showing that body fat distribution is influenced by genetic loci.<sup>6-8</sup> Genome-wide association studies (GWAS) were conducted to identify the loci linked to waist circumference and waist-hip ratio in the Caucasian population.<sup>9</sup>  
<sup>10</sup> Among the reported loci, we have reported that the rs1558902 and rs1421085 genotypes of the fat mass- and obesity-associated gene (*FTO*) were significantly associated with VFA as well as with subcutaneous fat area (SFA) and body mass index (BMI).<sup>11</sup>

GWAS and meta-analysis of GWAS have also identified metabolic syndrome trait-associated genetic variations, including obesity, type 2 diabetes, dyslipidemia, and hypertension.<sup>12</sup> We have previously reported that among the single nucleotide polymorphisms

(SNPs) susceptible to obesity,<sup>13-15</sup> rs7498665 in the SH2B adaptor protein 1 (*SH2B1*) gene was associated with VFA,<sup>16</sup> and that among hypertension-susceptible SNPs,<sup>17, 18</sup> *CYP17A1* rs1004467 and *NT5C2* rs11191548 were significantly associated with both reduced VFA and SFA in women, indicating a genetic background to central obesity.<sup>19</sup> Visceral fat obesity is also a risk factor for the development of type 2 diabetes. Several studies have investigated the association of type 2 diabetes loci from GWAS with body fat and BMI.<sup>20-22</sup> However, there are few reports of the association between type 2 diabetes susceptibility SNPs and visceral fat accumulation.<sup>21, 23, 24</sup> Associations between type 2 diabetes susceptibility SNPs except those existed in the *FTO* gene and visceral fat mass determined by using more precise method, such as CT and magnetic resonance imaging (MRI), have not been elucidated yet. Therefore, we investigated the association between type 2 diabetes susceptibility SNPs and fat distribution (VFA and SFA) as determined by CT.

## MATERIALS AND METHODS

### Study subjects

In this study, we enrolled 1279 Japanese subjects from outpatient clinics as described previously.<sup>16, 19</sup> These patients agreed to undergo CT testing (in the supine position) to determine the VFA and SFA values at the umbilical level (L4–L5). Both VFA and SFA values

were calculated using the FatScan software program (N2system, Osaka, Japan).<sup>25</sup> The clinical characteristics of the subjects are summarized in Table 1. Metabolic syndrome and metabolic abnormalities were diagnosed according to the criteria released by the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome in April 2005.<sup>4, 5</sup> Written informed consent was obtained from each subject, and the protocol was approved by the ethics committee of each institution and of Kyoto University.

### **DNA extraction and SNP genotyping**

Genomic DNA was extracted using Genomix (Talent Srl, Trieste, Italy) from blood samples collected from each subject. We selected 23 SNPs identified as susceptibility loci for type 2 diabetes by GWAS<sup>26-33</sup> and constructed Invader probes (Third Wave Technologies, Madison, WI, USA) for the following SNPs: notch 2 (*NOTCH2*) rs10923931, thyroid adenoma-associated (*THADA*) rs7578597, peroxisome proliferator-activated receptor  $\gamma$  (*PPARG*) rs1801282, ADAM metalloproteinase with thrombospondin type 1 motif, 9 (*ADAMTS9*) rs4607103, insulin-like growth factor 2 mRNA-binding protein 2 (*IGF2BP2*) rs1470579, vascular endothelial growth factor A (*VEGFA*) rs9472138, JAZF zinc finger 1 (*JAZF1*) rs864745, cyclin-dependent kinase inhibitor 2A and cyclin-dependent kinase inhibitor 2B (*CDKN2A/CDKN2B*) rs564398 and rs10811661, hematopoietically expressed homeobox (*HHEX*) rs1111875 and rs5015480, transcription factor 7-like 2 (*TCF7L2*) rs7901695, potassium voltage-gated channel, KQT-like



subfamily, member 1 (*KCNQ1*) rs2237892, potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*) rs5215 and rs5219, exostosin 2 (*EXT2*) rs1113132, rs11037909, and rs3740878, melatonin receptor 1B (*MTNR1B*) rs10830963, dermcidin (*DCD*) rs1153188, TSPAN8 tetraspanin 8/leucine-rich repeat containing G protein-coupled receptor 5 (*TSPAN8/LGR5*) rs7961581, and *FTO* rs8050136 and rs9939609. The SNPs were genotyped using Invader assays as previously described.<sup>34</sup> The success rate of these assays was >99.0%.

### Statistical analysis

For the additive model, we coded the genotypes as 0, 1, or 2 depending on the number of copies of the risk alleles. Risk alleles refer to the type 2 diabetes-associated alleles, according to previous reports.<sup>26-33</sup> Multiple linear regression analyses were performed to test the independent effects of the risk alleles on BMI, VFA, and SFA by taking into account the effects of other variables (i.e., age and gender) that were assumed to be independent of the effect of each SNP. The values of BMI, VFA, and SFA were logarithmically transformed before multiple linear regression analysis. Odds ratios (ORs) and *P*-values adjusted for age, gender, and BMI were calculated using multiple logistic regression analysis with genotypes, age, gender, and log-transformed BMI as the independent variables. The Hardy–Weinberg equilibrium was assessed using the  $\chi^2$ -test.<sup>35</sup> All statistical analyses were performed using software R (<http://www.r-project.org/>). *P*-values were corrected by Bonferroni adjustment and  $P < 0.0021$

(0.05/23) was considered statistically significant.

## RESULTS

The clinical characteristics and genotypes of the subjects are listed in Tables 1 and 2, respectively. All SNPs remained in the Hardy–Weinberg equilibrium, except rs5215 and rs5219 in *KCNJ11* ( $P = 0.03$ ) and rs1153188 in *DCD* genes ( $P = 0.04$ ). The minor allele frequencies did not diverge from those reported in the HapMap database. The BMI, VFA, and SFA values for each SNP genotype are presented in Table 3. Multiple linear regression analyses of the anthropometric parameters with respect to the 23 SNPs analyzed are listed in Table 4. Two SNPs (rs8050136 and rs9939609) in the *FTO* gene were significantly associated with BMI in an additive model ( $P = 0.00088$  and  $0.0010$ , respectively). Since the results in Table 3 showed that the dominant model was the best-fit model, we analyzed the above 2 SNPs in the dominant model. Significant associations of BMI were observed with rs8050136 ( $P = 0.00052$ ) and rs9939609 ( $P = 0.00061$ ) in a dominant model.

There is no SNP associated with VFA. Only SNPs (rs8050136 and rs9939609) in the *FTO* gene were marginally associated with VFA ( $P < 0.05$ ). Two SNPs in the *FTO* gene were significantly associated with SFA ( $P = 0.00013$  at rs8050136 and  $P = 0.00017$  at rs9939609), while all other SNPs did not associate with SFA. BMI, VFA and SFA are known to be affected by gender; therefore, we compared SFA in men and women separately. Associations between

*FTO* rs8050136 and rs9939609 SNPs and BMI were not significant in either men ( $P = 0.045$  at rs8050136 and  $P = 0.048$  at rs9939609) or women ( $P = 0.0064$  at rs8050136 and  $P = 0.0075$  at rs9939609) in an additive model. Associations of *FTO* rs8050136 and rs9939609 SNPs with SFA were not significant in either men ( $P = 0.0066$  at rs8050136 and  $P = 0.0069$  at rs9939609) or women ( $P = 0.0058$  at rs8050136 and  $P = 0.0079$  at rs9939609) in an additive model. This negative association is most likely due to the decrease in the number of each genotype.

We conducted the power analysis of linear regression (additive model) with a significance level of 0.05, using age and gender as explanatory parameters. The estimated effect sizes per allele (regression coefficients) for logarithmically transformed BMI, VFA and SFA were 0.010, 0.017 and, 0.028, respectively, assuming from the values of rs8050136 and rs9939609 (Table 3). The power of our statistical test was calculated on the basis of these estimated effect sizes and by performing 10,000 simulations. When the allele frequency was assumed to be 0.2, the power was estimated to be 0.71 for BMI, 0.25 for VFA and 0.81 for SFA; however, when the allele frequency was assumed to be 0.1, the respective powers were estimated to be 0.47, 0.16, and 0.56.

Finally, we examined the association of these SNPs with impaired glucose tolerance. Although the number of subjects with impaired glucose tolerance was relatively small ( $n = 353$ ), we could replicate the association of rs10811661 in the *CDKN2A/B* gene ( $P = 0.049$ ),

rs2237892 in the *KCNQ1* gene ( $P = 0.00013$ ), and rs1113132 in the *EXT2* gene ( $P = 0.043$ ) with impaired glucose tolerance (Table 5).

## DISCUSSION

Obesity, especially visceral fat obesity, is an important risk factor for the development of metabolic syndromes, including type 2 diabetes. Recent GWAS revealed the genetic susceptibility factors for type 2 diabetes. The relationship between type 2 diabetes-associated SNPs and visceral fat obesity is of considerable interest. CT-based analyses are more accurate for evaluating the association of SNPs with visceral fat mass than BMI, waist circumference, or dual energy X-ray absorptiometry (DEXA)-based abdominal fat mass analysis.<sup>4,5</sup> Therefore, we investigated the association of type 2 diabetes susceptibility SNPs with VFA and SFA. We demonstrated that only SNPs in the *FTO* gene are associated with SFA and BMI, but not with VFA. *FTO* rs8050136 has been shown to be marginally associated with visceral fat mass measured by MRI in Germany ( $P = 0.05$ )<sup>36</sup> and rs9939609 with intra-abdominal adipose tissue estimated by DEXA in Danish ( $P = 4.7 \times 10^{-3}$ ).<sup>37</sup> SNP rs8050136 has been reported to be marginally associated with VFA measured by CT in African Americans ( $P = 0.05$ ), but not in Hispanic Americans.<sup>38</sup> Our study showed the weak association VFA and rs8050136 ( $P = 0.043$ ). Although the measurements of visceral fat were different, rs8050136 would be

associated with visceral fat accumulation. Since the simulation study showed the power of this study for VFA were relatively low ( $\alpha = 0.16$  to  $0.35$ ), large sample size would be necessary to confirm the association. SNP rs8050136 has been reported to be marginally associated with SFA measured by CT in African Americans ( $P = 0.038$ ) and in Hispanic Americans ( $P = 0.019$ ),<sup>38</sup> indicating that rs8050136 would be related with SFA in various populations.

Other type 2 diabetes susceptibility SNPs were not associated with BMI, VFA, or SFA. Pecioska *et al.* reported that among the type 2 diabetes loci (*SLC30A8*, *CDKN2A/B*, *CDKAL1*, *IGF2BP2*, *HHEX*, *PPARG*, *KCNJ11*, *TCFL2* and *FTO*), only *FTO* rs8050136 was associated with BMI, fat mass index (fat mass/height/height), and waist circumference.<sup>21</sup> Our results were in agreement with those reported by Pecioska *et al.* T allele of rs2237892 in the *KCNQ1* gene was reported to be associated with increased waist circumference ( $P = 0.043$ ).<sup>24</sup> However, the subjects with T-allele had lower VFA in our study. A lack of association of type 2 diabetes loci, and VFA and SFA may be due to the low power of this study. The associations between SNPs and type 2 diabetes were adjusted for BMI, age, and gender. Thus, SNPs associated with both obesity and type 2 diabetes would be excluded in the screening stage. Indeed, *FTO* was first discovered as a susceptibility gene for type 2 diabetes in an analysis that was not adjusted for BMI; after adjustment for BMI, the effect on type 2 diabetes was abolished.<sup>39</sup>

Most risk factors for type 2 diabetes are believed to act through perturbation of insulin

secretion rather than through insulin action (insulin resistance).<sup>40</sup> It is believed that *CDKN2A* and *CDKN2B* genes are involved in reducing  $\beta$ -cell mass, while *MTNR1B*, *TCFL2*, and *KCNJ11* genes may be involved in  $\beta$ -cell dysfunction. Only the *FTO* gene can act through insulin resistance caused by obesity. Our results, demonstrating no significant association of type 2 diabetes susceptibility SNPs with VFA or SFA, except for SNPs in the *FTO* gene, confirm the above mechanism for the development of type 2 diabetes.

In summary, we showed that 2 SNPs (rs8050136 and rs9939609) in the *FTO* gene are significantly associated with SFA and BMI and that other SNPs susceptible for type 2 diabetes are not associated with fat distribution. Our results suggest that only SNPs in the *FTO* gene are involved in the mechanism of insulin resistance.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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Table 1 General characteristics of the subjects

	Men	Women	Total
n	556	723	1279
Age (years)	49.4 ± 12.2	52.2 ± 11.3	51.0 ± 11.8
BMI (kg m <sup>-2</sup> )	30.2 ± 6.1	28.1 ± 5.3	29.0 ± 5.8
VFA (cm <sup>2</sup> )	155.3 ± 67.7	99.8 ± 53.6	123.9 ± 66.1
SFA (cm <sup>2</sup> )	206.7 ± 108.6	241.6 ± 97.2	226.5 ± 103.7
Waist circumference (cm)	97.5 ± 11.3	91.8 ± 10.3	94.2 ± 11.1
Prevalence of metabolic disease			
Dyslipidemia	293 (53%)	244 (34%)	537 (42%)
Hypertension	379 (68%)	452 (63%)	831 (65%)
Impaired fasting glucose	177 (32%)	176 (24%)	353 (28%)
Metabolic syndrome	248 (45%)	162 (22%)	410 (32%)

Data are shown as mean ± s. d.

Table 2 Type 2 diabetes-susceptible alleles and genotype frequencies in subjects

SNPs	Chr	Position (Build 36.3)	Nearby gene(s)	Alleles 1/2	Risk allele	Genotype (11/12/22)	Risk allele frequency	HWE <i>P</i> -value
rs10923931	1	120,319,482	<i>NOTCH2</i>	T/G	T	1/39/1239	0.02	0.23
rs7578597	2	43,586,327	<i>THADA</i>	T/C	T	1248/30/1	0.99	0.07
rs1801282	3	12,368,125	<i>PPARG</i>	G/C	C	0/60/1219	0.94	0.39
rs4607103	3	64,686,944	<i>ADAMTS9</i>	T/C	C	202/604/472	0.59	0.70
rs1470579	3	187,011,774	<i>IGF2BP2</i>	A/C	C	551/591/134	0.33	0.19
rs9472138	6	43,919,740	<i>VEGFA</i>	T/C	T	10/224/1044	0.08	0.59
rs864745	7	28,147,081	<i>JAZF1</i>	G/A	A	54/402/823	0.79	0.58
rs564398	9	22,019,547	<i>CDKN2A/B</i>	G/A	G	30/324/925	0.10	0.80
rs10811661	9	22,124,094	<i>CDKN2A/B</i>	T/C	T	420/598/261	0.52	0.07
rs1111875	10	94,452,862	<i>HHEX</i>	T/C	C	648/525/105	0.35	0.93
rs5015480	10	94,455,539	<i>HHEX</i>	T/C	C	895/355/29	0.20	0.37
rs7901695	10	114,744,078	<i>TCF7L2</i>	T/C	C	1182/96/1	0.03	0.51
rs2237892	11	2,796,327	<i>KCNQ1</i>	T/C	C	187/633/458	0.64	0.18
rs5215	11	17,365,206	<i>KCNJ11</i>	T/C	C	540/554/184	0.34	0.03
rs5219	11	17,366,148	<i>KCNJ11</i>	C/T	T	541/554/184	0.35	0.03
rs1113132	11	44,209,979	<i>EXT2</i>	G/C	C	161/590/527	0.64	0.84
rs11037909	11	44,212,190	<i>EXT2</i>	T/C	T	525/589/165	0.64	0.99
rs3740878	11	44,214,378	<i>EXT2</i>	A/G	A	513/595/171	0.64	0.94
rs10830963	11	92,348,358	<i>MTNR1B</i>	C/G	G	451/616/212	0.47	0.95
rs1153188	12	53,385,263	<i>DCD</i>	A/T	A	1211/65/3	0.98	0.04
rs7961581	12	69,949,369	<i>TSPAN8/LGR5</i>	T/C	C	828/392/57	0.23	0.23
rs8050136	16	52,373,776	<i>FTO</i>	C/A	A	769/443/65	0.18	0.91
rs9939609	16	52,378,028	<i>FTO</i>	T/A	A	768/446/64	0.18	0.94

Abbreviations: Chr, chromosome; HWE, Hardy–Weinberg equilibrium.

Table 3 Mean BMI, VFA, and SFA for 23 type 2 diabetes-susceptible SNPs

SNP ID	Nearby gene(s)	BMI (kg m <sup>-2</sup> )			VFA (cm <sup>2</sup> )			SFA (cm <sup>2</sup> )		
		Genotype			Genotype			Genotype		
		11	12	22	11	12	22	11	12	22
rs10923931	<i>NOTCH2</i>	25.8	28.7 ± 6.0	29.0 ± 5.8	122.6	122.8 ± 57.8	124.0 ± 66.4	120.4	229.1 ± 113.6	226.5 ± 103.4
rs7578597	<i>THADA</i>	29.0 ± 5.8	27.8 ± 4.7	33.2	123.7 ± 65.9	130.5 ± 71.9	235.8	226.5 ± 103.9	219.4 ± 96.2	385.6
rs1801282	<i>PPARG</i>	–	28.9 ± 5.6	29.0 ± 5.8	–	120.4 ± 82.0	124.1 ± 65.3	–	224.6 ± 92.0	226.5 ± 104.3
rs4607103	<i>ADAMTS9</i>	29.3 ± 6.9	29.0 ± 5.5	28.9 ± 5.6	127.4 ± 67.2	122.0 ± 68.2	125.1 ± 63.0	234.4 ± 115.4	224.9 ± 99.4	225.1 ± 104.0
rs1470579	<i>IGF2BP2</i>	29.0 ± 5.8	29.2 ± 5.9	28.1 ± 5.0	122.0 ± 66.6	127.0 ± 66.3	116.8 ± 60.4	230.3 ± 102.9	225.7 ± 104.3	215.2 ± 104.7
rs9472138	<i>VEGFA</i>	31.4 ± 4.6	28.4 ± 4.8	29.1 ± 6.0	134.1 ± 67.8	123.3 ± 66.8	124.0 ± 66.0	274.1 ± 102.6	212.8 ± 84.3	229.0 ± 107.3
rs864745	<i>JAZF1</i>	28.0 ± 5.6	29.3 ± 6.0	28.9 ± 5.7	131.7 ± 68.7	126.4 ± 66.2	122.2 ± 65.9	201.1 ± 96.7	230.6 ± 106.5	226.1 ± 102.7
rs564398	<i>CDKN2A/B</i>	29.8 ± 4.9	28.8 ± 5.4	29.0 ± 6.0	133.3 ± 65.5	124.8 ± 65.9	123.3 ± 66.3	226.2 ± 105.0	225.0 ± 99.6	227.0 ± 105.2
rs10811661	<i>CDKN2A/B</i>	29.2 ± 5.5	28.9 ± 6.0	28.9 ± 5.8	128.6 ± 67.7	121.5 ± 63.5	122.1 ± 69.3	231.6 ± 101.3	223.1 ± 104.9	225.7 ± 104.9
rs1111875	<i>HHEX</i>	29.1 ± 5.7	28.9 ± 5.7	29.1 ± 6.7	125.0 ± 65.2	123.7 ± 68.0	117.9 ± 62.5	230.6 ± 103.6	222.6 ± 101.5	220.7 ± 115.5
rs5015480	<i>HHEX</i>	29.0 ± 5.7	29.1 ± 6.2	28.2 ± 3.7	124.2 ± 65.1	124.3 ± 69.7	111.3 ± 52.6	228.3 ± 104.3	224.0 ± 104.0	198.6 ± 78.3
rs7901695	<i>TCF7L2</i>	29.1 ± 5.8	28.3 ± 5.1	33.2	124.9 ± 66.1	111.2 ± 65.4	235.8	227.6 ± 104.0	211.2 ± 99.3	385.6
rs2237892	<i>KCNQ1</i>	29.6 ± 6.5	29.1 ± 5.8	28.7 ± 5.4	120.5 ± 65.0	124.6 ± 65.2	124.5 ± 68.0	242.9 ± 117.7	225.0 ± 103.0	221.9 ± 98.2
rs5215	<i>KCNJ11</i>	29.0 ± 5.6	29.1 ± 6.1	28.5 ± 5.2	122.6 ± 64.3	125.6 ± 68.7	122.6 ± 63.6	228.9 ± 106.1	228.0 ± 103.1	214.4 ± 98.1
rs5219	<i>KCNJ11</i>	29.0 ± 5.7	29.1 ± 6.1	28.5 ± 5.2	122.7 ± 64.3	125.6 ± 68.7	122.6 ± 63.6	229.0 ± 106.1	228.0 ± 103.1	214.4 ± 98.1
rs1113132	<i>EXT2</i>	28.9 ± 6.2	29.2 ± 6.0	28.8 ± 5.4	128.4 ± 66.8	127.9 ± 69.7	118.0 ± 61.3	226.5 ± 107.4	228.4 ± 104.2	224.2 ± 102.2
rs11037909	<i>EXT2</i>	28.7 ± 5.4	29.3 ± 6.0	28.9 ± 6.1	118.0 ± 61.4	128.0 ± 69.7	128.3 ± 66.3	223.7 ± 101.9	229.2 ± 104.5	225.4 ± 107.0
rs3740878	<i>EXT2</i>	28.7 ± 5.4	29.3 ± 6.0	28.9 ± 6.1	117.9 ± 61.7	128.0 ± 68.7	128.1 ± 69.0	222.9 ± 101.9	230.2 ± 104.7	224.1 ± 106.0
rs10830963	<i>MTNR1B</i>	29.2 ± 5.9	29.0 ± 5.9	28.8 ± 5.2	124.8 ± 66.8	123.4 ± 66.2	123.6 ± 64.6	227.7 ± 105.7	224.5 ± 103.1	229.6 ± 101.8
rs1153188	<i>DCD</i>	29.0 ± 5.8	28.4 ± 5.1	32.1 ± 2.2	124.4 ± 66.4	112.8 ± 60.9	154.4 ± 33.5	227.0 ± 103.6	214.3 ± 107.4	253.7 ± 64.9
rs7961581	<i>TSPAN8/LGR5</i>	28.8 ± 5.4	29.5 ± 6.6	28.2 ± 4.9	122.4 ± 63.6	127.3 ± 70.4	121.9 ± 72.8	225.3 ± 102.7	230.3 ± 107.8	215.1 ± 90.2
rs8050136	<i>FTO</i>	28.5 ± 5.7	29.7 ± 5.8	29.8 ± 6.0	120.3 ± 65.1	129.7 ± 67.3	128.0 ± 68.2	219.0 ± 103.8	235.6 ± 99.0	252.6 ± 125.5
rs9939609	<i>FTO</i>	28.5 ± 5.7	29.7 ± 5.8	29.8 ± 6.1	120.3 ± 65.2	129.6 ± 67.1	128.5 ± 68.6	219.2 ± 103.9	235.2 ± 98.9	253.9 ± 126.1

Abbreviation: 11, allele1/allele1; 12, allele1/allele2; 22, allele2/allele2. Allele1 and allele2 of each SNP is indicated in Table 2.



Table 4 Quantitative association results for known type 2 diabetes risk alleles with BMI, VFA, and SFA

SNP ID	Nearby gene(s)	BMI			VFA			SFA		
		$\beta$	SE	<i>P</i> -value	$\beta$	SE	<i>P</i> -value	$\beta$	SE	<i>P</i> -value
rs10923931	<i>NOTCH2</i>	-0.007	0.012	0.53	0.026	0.037	0.49	-0.010	0.029	0.75
rs7578597	<i>THADA</i>	0.017	0.013	0.20	-0.030	0.042	0.48	-0.019	0.033	0.57
rs1801282	<i>PPARG</i>	-0.002	0.010	0.84	0.038	0.032	0.23	0.003	0.025	0.90
rs4607103	<i>ADAMTS9</i>	-0.001	0.003	0.74	0.004	0.010	0.67	-0.005	0.008	0.54
rs1470579	<i>IGF2BP2</i>	-0.004	0.003	0.18	-0.005	0.010	0.66	-0.011	0.008	0.16
rs9472138	<i>VEGFA</i>	-0.006	0.005	0.25	-0.004	0.016	0.83	-0.013	0.013	0.33
rs864745	<i>JAZF1</i>	0.000	0.004	0.96	-0.019	0.012	0.11	0.008	0.009	0.39
rs564398	<i>CDKN2A/B</i>	0.001	0.004	0.85	0.004	0.013	0.75	0.003	0.010	0.78
rs10811661	<i>CDKN2A/B</i>	0.004	0.003	0.22	0.015	0.009	0.12	0.012	0.007	0.12
rs1111875	<i>HHEX</i>	-0.003	0.003	0.33	-0.019	0.011	0.074	-0.017	0.008	0.047
rs5015480	<i>HHEX</i>	-0.003	0.004	0.49	-0.013	0.013	0.33	-0.016	0.010	0.12
rs7901695	<i>TCF7L2</i>	-0.009	0.008	0.27	-0.037	0.025	0.14	-0.033	0.020	0.095
rs2237892	<i>KCNQ1</i>	-0.006	0.003	0.053	0.003	0.010	0.73	-0.015	0.008	0.064
rs5215	<i>KCNJ11</i>	-0.002	0.003	0.43	0.000	0.010	1.00	-0.010	0.008	0.21
rs5219	<i>KCNJ11</i>	-0.003	0.003	0.39	0.000	0.010	0.97	-0.010	0.008	0.20
rs1113132	<i>EXT2</i>	-0.002	0.003	0.56	-0.015	0.010	0.13	-0.004	0.008	0.66
rs11037909	<i>EXT2</i>	-0.002	0.003	0.45	-0.016	0.010	0.11	-0.004	0.008	0.63
rs3740878	<i>EXT2</i>	-0.003	0.003	0.40	-0.015	0.010	0.13	-0.005	0.008	0.56
rs10830963	<i>MTNR1B</i>	-0.003	0.003	0.30	-0.008	0.010	0.41	0.002	0.008	0.80
rs1153188	<i>DCD</i>	-0.001	0.009	0.88	0.019	0.028	0.50	0.019	0.022	0.40
rs7961581	<i>TSPAN8/LGR5</i>	0.001	0.004	0.83	0.005	0.012	0.65	0.001	0.009	0.93
rs8050136	<i>FTO</i>	0.012	0.004	<b>0.00088</b>	0.023	0.011	0.043	0.035	0.009	<b>0.00013</b>
rs9939609	<i>FTO</i>	0.012	0.004	<b>0.0010</b>	0.024	0.011	0.035	0.034	0.009	<b>0.00017</b>

Data were derived from a linear regression analysis. BMI, VFA, and SFA were adjusted for age and gender, and log-transformed for the analysis.

Table 5 Association of type 2 diabetes-associated loci alleles and impaired fasting plasma glucose

SNP ID	Nearby gene(s)	Genotype(11/12/22)		<i>P</i> -value	OR (95% CI)
		Case (n = 353)	Control (n = 926)		
rs10923931	<i>NOTCH2</i>	0/8/345	1/31/894	0.34	0.67 (0.29 – 1.52)
rs7578597	<i>THADA</i>	345/8/0	903/22/1	0.96	1.02 (0.45 – 2.29)
rs1801282	<i>PPARG</i>	0/11/342	0/49/877	0.08	1.87 (0.92 – 3.78)
rs4607103	<i>ADAMTS9</i>	56/170/127	146/434/345	0.72	0.97 (0.80 – 1.16)
rs1470579	<i>IGF2BP2</i>	147/163/41	404/428/93	0.33	1.10 (0.91 – 1.35)
rs9472138	<i>VEGFA</i>	3/67/283	7/157/761	0.17	1.24 (0.91 – 1.68)
rs864745	<i>JAZF1</i>	13/109/231	41/293/592	0.48	1.09 (0.86 – 1.37)
rs564398	<i>CDKN2A/B</i>	8/79/266	22/245/659	0.13	0.82 (0.63 – 1.06)
rs10811661	<i>CDKN2A/B</i>	129/165/59	291/433/202	<b>0.049</b>	1.20 (1.00 – 1.44)
rs1111875	<i>HHEX</i>	184/131/37	464/394/68	0.64	1.05 (0.86 – 1.28)
rs5015480	<i>HHEX</i>	248/92/13	647/263/16	0.51	1.09 (0.85 – 1.40)
rs7901695	<i>TCF7L2</i>	323/30/0	859/66/1	0.22	1.34 (0.84 – 2.14)
rs2237892	<i>KCNQ1</i>	40/167/146	147/466/312	<b>0.00013</b>	1.47 (1.21 – 1.79)
rs5215	<i>KCNJ11</i>	141/158/53	399/396/131	0.28	1.11 (0.92 – 1.33)
rs5219	<i>KCNJ11</i>	142/158/53	399/396/131	0.29	1.10 (0.92 – 1.33)
rs1113132	<i>EXT2</i>	39/156/157	122/434/370	<b>0.043</b>	1.22 (1.01 – 1.49)
rs11037909	<i>EXT2</i>	156/155/42	369/434/123	0.067	1.20 (0.99 – 1.45)
rs3740878	<i>EXT2</i>	152/159/42	361/436/129	0.051	1.21 (1.00 – 1.47)
rs10830963	<i>MTNR1B</i>	120/174/59	331/442/153	0.51	1.06 (0.88 – 1.28)
rs1153188	<i>DCD</i>	333/20/0	878/45/3	0.99	1.00 (0.59 – 1.69)
rs7961581	<i>TSPAN8/LGR5</i>	233/105/14	595/287/43	0.47	0.92 (0.73 – 1.16)
rs8050136	<i>FTO</i>	202/131/19	567/312/46	0.82	1.03 (0.82 – 1.28)
rs9939609	<i>FTO</i>	202/132/19	566/314/45	0.75	1.04 (0.83 – 1.29)

Data were derived from logistic regression analysis. *P*-value and ORs were adjusted for age, gender, and BMI. BMI was log-transformed for the analysis.